Biomarkers in development of psychotropic drugs

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During recent years biomarkers have received increasing attention in all medical specialties, but it is particularly in the field of psychiatry that biomarkers are expected to gain a more specific position. Up to now, despite several decades of intensive research, the biology of psychiatric disorders remains more or less elusive, and is more challenging than in any other spectrum of diseases in terms of diagnostic diversity, pathophysiology, and response to treatment.

The latter is particularly important since, despite the availability of a set of therapeutic tools including pharmacotherapy, psychotherapy, and biological therapies, there are still unmet needs regarding onset of action, stability of response, and further improvement of the

Biomarkers have been receiving increasing attention, especially in the field of psychiatry. In contrast to the availability of potent therapeutic tools including pharmacotherapy, psychotherapy, and biological therapies, unmet needs remain in terms of onset of action, stability of response, and further improvement of the clinical course. Biomarkers are objectively measured characteristics which serve as indicators of the causes of illnesses, their clinical course, and modification by treatment. There exist a variety of markers: laboratory markers which comprise the determination of genetic and epigenetic markers, neurotransmitters, hormones, cytokines, neuropeptides, enzymes, and others as single measures; electrophysiological markers which usually comprise electroencephalography (EEG) measures, and in particular sleep EEG and evoked potentials, magnetic encephalography, electrocardiogram, facial electromyography, skin conductance, and others; brain imaging techniques such as cranial computed tomography, magnetic resonance imaging, functional MRI, magnetic resonance spectroscopy, positron emission tomography, and single photon emission computed tomography; and behavioral approaches such as cue exposure and challenge tests which can be used to induce especially emotional processes in anxiety and depression. Examples for each of these domains are provided in this review. With a view to developing more individually tailored therapeutic strategies, the characterization of patients and the courses of different types of treatment will become even more important in the future. .

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clinical course. Psychiatric disorders still show a wide diagnostic variability, for example, the differential diagnosis of early uni- vs bipolar disorders, the differentiation within the schizoaffective spectrum (between the bipolar and schizophrenic pole) or the comorbidity of anxiety spectrum disorders and depressive spectrum disorders. Hence, for an apparently similar phenotype, the relevant biomarkers may vary considerably, leading to a blurred relationship between distinct biomarkers and psychopathologically defined nosological entities. Biomarkers are regularly determined by technical, somewhat "objective" means using chemical or physical measures.[1] In contrast, the clinical diagnosis of any psychiatric disease and monitoring of the clinical course either during the patient's everyday life or during clinical trials of therapeutic interventions is still carried out by psychometric and somewhat "subjective" means. Despite a considerable and immense set of psychological measures, the rating within each test is done by psychiatrists and psychologists, who of course are trained, but still subject to their individual points of view. This incurs an additional considerable risk of variation.

Importantly, the stability of diagnoses varies over the long-term course of psychiatric diseases.[2] Hence, even variability between raters at the same time point can occur, and during extended periods of observation distinct measures may vary considerably. This leads to the problem of whether pathological findings represent a "state" or "trait" phenomenon, whereby "state" may represent either a stable condition apparent at the onset of the disease or a biological "scar" as late sequela of this disease. Currently some biomarkers are regarded as state markers such as genetics and related findings, in addition, several markers are putative trait markers. Both state and trait markers carry distinct information which provides the possibility of characterizing treatment outcome better than mere subjective measures.

Definition

The term "biomarker" is not always appropriately used, given the great diversity of methods and investigational procedures to identify the origin or "state" of psychiatric disorders. Moreover, for drug development it also appears necessary to identify "trait" alterations; this is of importance for identification of parameters monitoring the intrinsic course of illness on one hand and predicting the efficacy of treatment procedures on this intrinsic course on the other hand. From this point of view for biomarkers individual dynamic responsiveness to interventions is also interesting. Absolute measures are helpful in identifying, eg, alterations in comparison of patients vs controls. However, of further interest is the way the individual response has to be classified: within the physiological bandwidth of homeostasis or at the borders of individual regulatory capacity.

According to Frank and Hargreaves,[1] biomarkers are characteristics which are objectively measured and evaluated as an indicator of the intrinsic causes of illnesses, the clinical course, and its modification by treatment. In this context the authors point to the differentiation of clinical end points of treatment and surrogate end points: the former is for psychiatric approaches reflected by behavior and subjective feelings. For the latter the surrogate end point substitutes a clinical end point, to predict clinically wanted or unwanted effects. In addition, different types of biomarkers can in general be classified as shown in *Table I* [3]:

- Type 0 biomarkers are markers of the intrinsic cause of an illness and its longitudal course
- Type 1 markers identify the effects of an intervention by a specific drug action
- Type 2 markers are surrogate end points which predict the clinical course.

Table I. Types of biomarkers.

Another aspect comprises the terms sensitivity and specificity. Sensitivity and specificity are statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of measures or markers which correctly identify a condition, specificity measures the proportion of negative measures, which resembles the concept of Type I and Type II errors.[4] In the spectrum of biomarkers there is considerable variability with regard to sensitivity and specificity.

Up to now, and especially in the past decade, a multitude of procedures have been developed, which may be listed as follows (adapted from ref 5, but not an exhaustive list of approaches -*Table II)*:

• Laboratory markers which comprise the determination of genetic and epigenetic markers, transmitters, hormones, cytokines, neuropeptides, enzymes, and others as single measures; this approach is also suited to reflecting the investigation of complex biological systems in its approximated entirety which is frequently described as a genome, proteome, and metabolome[6]
• Electrophysiological markers which regularly comprise, eg, electroencephalography (EEG) measures[7] (and particularly sleep EEG and evoked potentials),[8] magnetic encephalography, electrocardiography, and in particular heart rate variability analyses,[9] facial electromyography analysis for emotion processing,[10] skin conductance, and others
• Brain imaging techniques like cranial computed tomography, magnetic resonance imaging (MRI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single-photon emission computed tomography (SPECT)[11,12]
• Behavioral approaches such as cue exposure and challenge tests which can be used to induce or monitor especially emotional processes in anxiety and depression.[13,14]

Table II. Targets of biomarkers.

In clinical trials in the development of new drugs for psychiatric diseases, at a very early stage the analysis of concentrations and the presence or absence of markers are important approaches for characterizing, in addition to the behavioral characteristics of efficacy, the global "phenome" of the patient's condition.

Examples of biomarkers in depression, anxiety disorders, and schizophrenia

Genetics

Modern antidepressant drugs are, in terms of efficacy, largely similar to drugs discovered several years ago. The development of new treatments for depression is limited by the availability of validated human biomarker models.[15] Family studies have revealed that the clinical response to antidepressant treatment shows more similarities within one family compared with controls, which indicates that uptake, metabolism, transport of drugs, and receptor binding is subjected to genetically controlled enzymes, receptor expression, and others factors.

Monoamine transporters, including the serotonin, norepinephrine, and dopamine transporters are important in regulating neurotransmission by uptake of respective transmitters released from nerve terminals. Regarding serotonin transporter gene length polymorphisms, Caspi and colleagues[16] concluded that in interaction with stressful life events the genetic variation in the promoter region plays a role in predisposition to major depression. In the context of selective serotonin reuptake inhibitors in treatment of depression and the well-established link between stressful life events and depression, this finding offered a convincing biological link. This result, however, could not be confirmed by metanalyses of 14 studies[17] and a birth cohort study in nearly 900 participants[18]: neither a risk elevation nor stable gene x environment interactions were able to be proven. These findings question the suitability of single-gene expression alterations for differentiation of patients in clinical trials. Genome-wide association studies point to multiple loci which in combination with additional clinical characteristics may be better suited for predicting treatment responses.[19] One of the largest recent cohort studies for evaluation of treatment algorithms is the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial, which provided DNA from nearly 2000 patients with nonpsychotic depression. Variants in the serotonin 2A receptor, the subunit of the glutamate-kainate receptor (GRIK4) the potassium channel (KCNK2) the chaperone FKBP5, a protein important for HPA axis regulation, were associated with citalopram treatment outcome.[20,21] For example, participants who were homozygous for the A allele of the serotonin 2A receptor had an 18% reduction in absolute risk of having no response to treatment.[22] Analyzing the BDNF ValMet66 polymorphism, no evidence of an association with treatment outcome in STAR*D could be found.[23]

There is also evidence for a complex inheritance with multiple genes in the etiology of panic disorder. So far it has not been possible to identify single major responsible genes. Again, several genes of classical neurotransmitter systems have been reported to be associated, eg, genes of the serotonin transporter length polymorphisms, of the monoamine oxidase A, catechol-O-methyltransferase, adenosine receptor, and cholecystokinin B.[24] After treating healthy volunteers with escitalopram, the induction of panic-like anxiety by cholecystokinin tetrapeptide was significantly more pronounced in the short/short genotype subjects during escitalopram vs placebo pretreatment, and no inhibitory effect of escitalopram upon panic-like symptoms elicited by choleystokinin tetrapeptide could be demonstrated.[14] These findings support the notion that gene x treatment effects are highly complex and subject to a variety of influential factors.

Of special interest is the pathophysiology of hypothalamo-pituitary-adrenocortical (HPA) axis regulation in depression and anxiety disorders: corticotropin-releasing hormone (CRH) related peptides, gluco- and mineralocorticoids and their receptors play an important role in behavioral, endocrine, and autonomic responses to stress, which is thought to be important in depression and anxiety. The chaperone FKBP5, a protein involved in HPA axis regulation, has been shown to mediate interaction effects with other polymorphisms.[21] Selective antagonists have been used experimentally to elucidate the role of CRH-related peptides, but up to now the development of specific drugs has been challenging[25,26] and tests of these compounds in genetically well-characterized patient samples remain to be tested.

Schizophrenia is also the result of genetic alterations. However, genetic research has been impaired by the lack of disease-specific biomarkers. Despite an estimated 70% to 80% heritability of schizophrenia, nongenetic factors considerably modify the incidence and course of this disease, which complicates the identification of susceptibility genes.[27] Genes such as *DISC1* include existing targets for drug development in schizophrenia and depression,[28] but are not specific for schizophrenia.

The wide interindividual variability in clinical efficacy and tolerability of antipsychotic medications led investigators to relate not only efficacy of antipsychotic medications but side-effect profiles to pharmacogenetic factors.[29] However, up to now, only a few genome-wide association studies, eg, the CATIE trial with atypical antipsychotic treatment, are available which might lead to novel genes important for the efficacy of antipsychotics.[30]

Pharmacogenetics

In the context of pharmacogenetics, there was a goal of establishing individualized pharmacotherapy.[31] Genes encoding for enzymes involved in phase 1 metabolism are mainly cytochrome P450 (CYP) enzymes, which are known to contain a large variety of functional polymorphisms that significantly alter their metabolic activity. Common CYP polymorphisms can be distinguished by their effects upon metabolic rate, identifying the enzyme as slow (poor metabolizers), rapid (extensive metabolizers), or ultrarapid (ultrarapid metabolizers).[32] In particular, CYP2D6, a hepatic enzyme involved in the metabolism and elimination of antidepressants and antipsychotics, has been thoroughly investigated and associated with loss of efficacy or the potential to develop toxic reactions. Individuals presenting CYP2D6 PM variants are more likely to develop extrapyramidal side effects and weight gain. Kirchheiner and Rodriguez-Antona[33] showed that CYP2D6 and CYP2C19 metabolic rates may have an important influence upon the required doses of antidepressants and antipsychotics. This is an example for the clinical use of pharmacogenetics, especially when combined with clinical informations.

The geographical distribution of *CYP2D6* variants is heterogenous, supporting the notion that metabolic polymorphisms account for a significant part of variability in response to medications. Functional polymorphisms have been observed also in genes coding for CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes. Whereas CYP2C19 may be clinically relevant for the metabolism of antidepressants, CYP1A2 and CYP3A4 are major metabolic pathways of most commonly used antipsychotics, eg, olanzapine, risperidone, aripiprazole, and clozapine. Slow *CYP1A2* variants have been associated with increased risk of drug-induced side effects. Since smoking can induce CYP1A2 activity, this example of a gene x environment interaction may have clinical significance: individuals with CYP1A2 rapid phenotypes who smoke are known to experience an impaired response to treatment with clozapine, a CYP1A2 substrate. Few reports have investigated *CYP3A4*, *CYP2C9*, and *CYP2C19* functional variants and their influence on clinical outcome, with only some reference to the influence of *CYP2C19* variants on therapeutic doses of antidepressants.[34] Whereas it has been postulated that clinical trials should include measurements of blood concentrations during drug development to generate more valid data about the relationship between drug concentrations and clinical outcomes under controlled conditions,[35] up to now no studies have reported on the prospective use of CYP genotyping in clinical practice.[36]

Regarding the pharmacodynamics of the respective types of drugs, genetic polymorphisms in serotonin, noradrenaline, and dopamine receptors have been extensively investigated. Again, no single but multiple genes play a role in complex phenotypes, including the clinical response to medication. Thus, a multiple candidate gene approach has recently been adopted in pharmacogenetics. The new field of pharmacogenomics using DNA microarray analysis, which focuses on the genetic determinants of drug response at the level of the entire human genome, is important for development and prescription of, eg, safer and more effective individually tailored antipsychotics.[37]

Biochemistry

Studies with profiling experiments on brain physiology have to rely largely on postmortem analyses, which carry the risk of artefacts. Approaches to parallel alterations of the transcriptome, proteome, and metabolome in brain to findings in blood and cerebrospinal fluid (CSF) are possibly capable of providing experimental evidence for molecular findings in psychiatric disorders which help to identify also treatment responses.[6] Using proteomics to investigate distinct protein patterns is promising to improve the biology of psychiatric disorders and to identify biomarkers.[38] Also, knowledge of biochemical pathways can provide disease marker information required for drug development and improved patient treatment. Therefore, approaches to identifying pathways that affect depression-, anxiety- and schizophrenia-like phenotypes could be important.[39] Due to the close proximity of CSF to the brain, pathological brain processes are more likely to be reflected in CSF than in blood or saliva,[40] and especially new tools like capillary electrophoresis-mass spectrometry in proteome analysis[41] could also reveal new proteins in CSF that are suited as biomarkers for treatment responses.

Neuroendocrinology and hypothalamic-pituitary-adrenal axis alterations

Particularly in depression, but also in anxiety disorders, frequently alterations of the hypothalamic-pituitary-adrenal (HPA) axis are observed. Besides steroids, numerous other factors regulate HPA axis responsiveness: at the hypothalamic level corticotrophin-releasing hormone (CRH) and receptors such as the CRH1- and CRH2-receptor,[42] modulators such as agonistic vasopressin[43] and antagonistic atriopeptins [44,45] are involved in the central regulation of HPA activity. At the molecular level, glucocorticoid receptor polymorphisms may be associated either with hypofunction or hyperfunction which could contribute to these findings.[46] Other factors are the influences of steroids like estrogen and progesterone. However, immune molecules, such as interleukins and cytokines, also activate the HPA axis and alter brain function, including cognition and mood.[47]
Regarding treatment outcome, pivotal studies have been conducted in the past, applying the dexamethasone-induced suppression of HPA activity, the CRH stimulation test of HPA activity, and the combined dexamethasone-CRH test to predict treatment reponse.[48] In an investigation by Schüle et al[49] the attenuation of HPA axis activity after 1 week of antidepressant pharmacotherapy was significantly associated with subsequent improvement of depressive symptoms. Also, other single tests revealed a predictive potency of the dexamethasone-CRH test.[50] These findings are in line with studies reported by Ising et al,[51] who found normalized HPA activity in a subsequent dexamethasone-CRH test 2 or 3 weeks after the first test at beginning of treatment with an association of psychopathological improvement after 5 weeks. Interestingly, the effects of CRH-1 receptor antagonists[25] and glucocorticoid receptor antagonists[52] could not be predicted by defined alterations of HPA activity before treatment. In line with this, HPA axis activity also did not predict the efficacy of cortisol synthesis inhibitors in treatment of depression.[53]

Sleep electroencephalography

Sleep electroencephalogram (EEG) analysis provides markers of depression[54,55] and for antidepressant therapy.[8] For a long time it has been known that EEG activity is altered by drugs. Quantitative EEG analysis helps to delineate effects of antidepressants on brain activity. Elevated rapid eye movement (REM) density, which is a measure of frequency of REM, characterizes an endophenotype in family studies of depression. For example, for paroxetine REM density after 1 week of treatment was a predictor of treatment response.[56]
Most antidepressants suppress REM sleep in depressed patients and normal controls, but REM suppression appears not to be crucial for antidepressant effects. Sleep EEG variables like REM latency and other variables were shown to predict the response to treatment with an antidepressant or the course of the depressive disorder. Some of these predictive sleep EEG markers of the long-term course of depression appear to be closely related to hypothalamo-pituitary-adrenocortical system activity.[8,54]

Challenge studies

To experimentally induce fear, or panic anxiety, several approaches with a large variety of agents have been conducted for further elaboration of the physiological basis of pathologic anxiety. Targets are the identification of more effective anxiolytic compounds avoiding addictive

effects. In early human clinical psychopharmacology, a variety of challenge paradigms were investigated to establish the proof of concept in healthy volunteers. Different types of models for patients and healthy volunteers are available *(Table III)*.

However, these challenge paradigms fulfil the requirements of test-retest consistence and standardized responsiveness to reference drugs only in part. Most of them have been developed for the purpose of pathophysiological studies,[58] using rating instruments validated for clinical practice. Adapting these models to the requirements of pharmaceutical trials involves possibly a wider use of other biomarkers, and better characterization has to be carried out.[59]

Whether human models can significantly enhance and accelerate phase I studies remains elusive. For example, experimental panic induction with cholecystokinin tetrapeptide (CCK4) is considered a suitable model to investigate the pathophysiology of panic attacks and a variety of studies in patients and healthy volunteers have been conducted. Some clinical trials have proven the validity of CCK4 studies in selective serotonin reuptake inhibitors,[60] benzodiazepine trials[61] and experimental studies with neuropeptides and neurosteroids.[44,62] In contrast, CCK4 antagonist studies[63,64] have shown equivocal effects in patients with panic disorder. Moreover, studies in healthy men showed stimulatory effects of escitalopram upon panic symptoms elicited by choleystokinin tetrapeptide. These findings question the potential usefulness of this panic model for proof-of-concept studies.[14]

Imaging

Brain imaging represents a tool to characterize state and trait markers, also in disorders with an episodic course such as schizophrenia and bipolar disorder. An integrated approach to support diagnostic processes may lead to a more accurate classification of depression.[11] Results of functional magnetic resonance imaging (fMRI) indicate that both gray and white matter have diagnostic and prognostic potential in major depression and may provide an initial step towards the use of markers to predict efficacy of pharmacologic treatment.[65] Besides structural analyses, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are used to identify alterations of neurotransmitters and their respective receptors in specific regions of the brains. Magnetic resonance spectroscopy (MRS) literature supports the presence of brain metabolic alterations in relation to individual mood state. An analysis of 31P-MRS studies regarding brain energetic status and phospholipid metabolism provided support for state-specific alterations in bipolar disorder.[66] More generally, evidence for an abnormal brain energy metabolism in mood disorders was found. Metabolic aberrations may be intrinsic since, for example, brain intracellular pH determined by 31P-MRS is decreased in medication-free bipolar patients in manic, depressed, and euthymic mood states.[12]

Anxiety, and in particular panic disorder, has been extensively investigated to link episodic pathological

Panicogen	Heart rate stimulation	Dyspnea	Respiratory stimulation	HPA stimulation	NE stimulation
Cognitive	+	+	+	-	-
Lactate	+	+	+	-	-
Bicarbonate	-	+	+	-	-
CO_2	?	+	+	-	-
Isoproterenol	+	+	+	?	?
Caffeine	+	-	+	+	-
Cholecystokinin-4	+	+	(+)	+	-
Pentagastrin	+	+	(+)	+	?
Yohimbine	+	-	-	+	+
mCCP	+	-	-	+	-
Fenfluramine	+	-	-	+	-
β-Carboline	+	-	-	+	+
Flumazenil	?	-	-	-	?

Table III. Panic anxiety-inducing agents.
Adapted from ref 57: Nutt D, Lawson C. Panic attacks: a neurochemical overview of models and mechanisms. *Br J Psychiatry*. 1992;160:165-178. Copyright © Royal College of Psychiatrists 1992

symptoms to underlying biological mechanisms. It is hypothesized that respiratory dysregulation persists as a trait finding, also in the asymptomatic state.[67] Patients with panic disorder are susceptible to panic attacks precipitated by challenges like sodium lactate infusion, carbon dioxide inhalation, and hyperventilation *(Table III)*. Intravenous infusion of 0. 5 mol/L sodium lactate with 70 mL/kg body weight produces marked physiologic and psychologic symptoms in panic patients but less frequently in healthy controls.[58] Also in 1-h MRS studies lactate infusion was used as a physiological challenge to investigate brain metabolism. When the distribution of lactate increases was assessed, abnormal brain lactate increases were estimated as tissue-based due to brain metabolic mechanisms. However, persistent brain lactate rises in panic patients during treatment with, eg, fluoxetine or gabapentin, indicate that brain lactate increases are possibly independent of metabolic challenges, which questions their suitability as markers.[66]

Only a few fMRI studies have investigated the brain activation patterns following CCK4 administration. CCK4-induced anxiety was accompanied by strong and robust activation in various areas. Analysis for placebo and anticipatory anxiety generated no significant differences, and overall functional responses did not differ between panickers and nonpanickers.[68] Up to now, no fMRI studies have been conducted to predict treatment response.

In patients with schizophrenia especially, studies of specific receptors, such as the dopamine D2 receptor, before and after administration of an antipsychotic, provide a means to determine receptor occupation. PET findings of high D2-receptor occupation in the striatum of responders to different antipsychotics provided clinical support for the dopamine hypothesis of antipsychotic drug action. Patients with extrapyramidal syndromes (EPS) show a higher occupancy—over 80%—than patients with no EPS. The PET-defined interval for an optimal antipsychotic drug treatment has been used in dose recommendations for typical and atypical antipsychotics. Interestingly, currently available PET ligands are not selective for the five dopamine receptor subtypes.[69] However, up to now PET can be used to predict and monitor extrapyramidal side effects of antipsychotic treatment rather than therapeutic efficacy.[70]

Summary

In this overview some biomarkers for future development of psychopharmaceutical drugs have been exemplified for antidepressants, anxiolytics, and antipsychotics. Due to the trend to develop more individually tailored therapeutic strategies, the characterization of patients and the course of treatment by different aspects will become more important in the future. A better description of state and trait characteristics should enable us to focus on a more specific individual "phenome" that is to be treated. In applying biomarkers to therapeutic drug development, additional aspects have to be taken into account: the increasing frequency of psychiatric diagnoses and especially of depression and anxiety and a trend to denosologization during the past decades regarding "depressive syndromes" and "anxiety spectrum disorders." To predict or monitor treatment responses more precisely, biomarkers will need to characterize the patient's condition in an integrated manner. ❑

REFERENCES

1. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. *Nat Rev Drug Discov*. 2003;2:566-580.
2. Möller HJ, Jäger M, Riedel M, Obermeier M, Strauss A, Bottlender R. The Munich 15-year follow-up study (MUFSSAD) on first-hospitalized patients with schizophrenic or affective disorders: Assessing courses, types and time stability of diagnostic classification. *Eur Psychiatry*. 2010;196:460-466.
3. Lesko LJ, Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decisionmaking: criteria, validation, strategies. *Annu Rev Pharmacol Toxicol*. 2001;41:347-366.
4. Spilker B. *Guide to Clinical Trials*. Philadelphia, PA: Lippincott-Raven Publishers; 1996.
5. Bieck PR, Potter WZ. Biomarkers in psychotropic drug development: integration of data across multiple domains. *Annu Rev Pharmacol Toxicol*. 2005;45:227-246.
6. Schwarz E, Bahn S. The utility of biomarker discovery approaches for the detection of disease mechanisms in psychiatric disorders. *Br J Pharmacol*. 2008;153(suppl 1):S133-S136.
7. Leiser SC, Dunlop J, Bowlby MR, Devilbiss DM. Aligning strategies for using EEG as a surrogate biomarker: aA review of preclinical andclinical research. *Biochem Pharmacol*. 2011;81:1408-1421.
8. Steiger A, Kimura M. Wake and sleep EEG provide biomarkers in depression. *J Psychiatr Res*. 2010;44:242-252.
9. Seier FE, Kellner M, Yassouridis A, Heese R, Strian F, Wiedemann K. Autonomic reactivity and hormonal secretion in lactate-induced panik attacks. *Am J Physiol*. 1997;272:H2630-H638.
10. Hinkelmann K, Yassouridis A, Mass R, et al. CCK-4: pPsychophysiological conditioning elicits features of spontaneous panic attacks. *J Psychiatr Res*. 2010;44:1148-1153.
11. Hahn T, Marquand AF, Ehlis AC, Dresler T, et al. integrating neurobiological markers of depression. *Arch Gen Psychiatry*. 2010;68:361-368.
12. Wong DF, Gründer G, Brasic JR. Brain imaging research: does the science serve clinical practice? *Int Rev Psychiatry*. 2007;19:541-558.

Biomarcadores en el desarrollo de fármacos psicotrópicos

Los biomarcadores han estado recibiendo creciente atención, especialmente en psiquiatría. En contraste con la disponibilidad de potentes herramientas terapéuticas incluidas la farmacoterapia, la psicoterapia y las terapias biológicas, aun hay necesidades insatisfechas en términos del comienzo de la acción, la estabilidad de la respuesta y una mayor mejoría del curso clínico. Los biomarcadores son características mensurables objetivamente que sirven como indicadores de las causas de la enfermedad, su curso clínico y la modificación por el tratamiento. Existe una variedad de biomarcadores: marcadores de laboratorio que incluyen la determinación de marcadores genéticos y epigenéticos, neurotransmisores, hormonas, citoquinas, neuropéptidos, enzimas, y otras mediciones aisladas; marcadores electrofisiológicos que habitualmente incluyen mediciones electroencefalográficas (EEG), y en especial EEG del sueño y potenciales evocados, encefalografía magnética, electrocardiograma, electromiografía facial, conductancia de la piel y otros; técnicas de imágenes como la tomografía computada craneal, imágenes de resonancia magnética, resonancia magnética funcional, espectroscopia por resonancia magnética, tomografía por emisión de positrones y tomografía computada por emisión de fotón único, y aproximaciones conductuales como la exposición a señales y las pruebas de desafío, las que pueden ser empleadas especialmente para inducir procesos emocionales en la ansiedad y la depresión. En esta revisión se entregan ejemplos de cada una de estas áreas. Con una perspectiva de desarrollar estrategias terapéuticas más a la medida de cada individuo, la caracterización de pacientes y los cursos de diferentes tratamientos llegarán a ser aun más importantes a futuro.

Les biomarqueurs dans le développement des psychotropes

Une attention croissante est portée sur les biomarqueurs, en particulier dans le domaine de la psychiatrie. Alors que des outils thérapeutiques puissants comme la pharmacothérapie, la psychothérapie et les traitements biologiques sont disponibles, des besoins non satisfaits persistent en termes de mise en œuvre de la stratégie, de stabilité de la réponse et d'amélioration ultérieure de l'évolution clinique. Les biomarqueurs sont des caractéristiques mesurées objectivement, servant d'indicateurs des causes des pathologies, de leur évolution clinique et des changements dus au traitement. Il existe un grand nombre de marqueurs : les marqueurs de laboratoire qui comprennent la détermination des marqueurs génétiques et épigénétiques, les neurotransmetteurs, les hormones, les cytokines, les neuropeptides, les enzymes et d'autres, comme mesures simples ; les marqueurs électrophysiologiques habituellement représentés par l'électroencéphalographie (EEG) et en particulier l'EEG du sommeil et les potentiels évoqués, l'encéphalographie magnétique, l'électrocardiogramme, l'électromyographie faciale, la conductance cutanée et d'autres ; les techniques d'imagerie cérébrale comme le scanner cérébral, l'imagerie par résonance magnétique, l'IRM fonctionnelle, la spectroscopie par résonance magnétique, la tomographie par émission de positons et la tomographie par émission monophotonique (SPECT) ; et les approches comportementales comme l'exposition à un signal et les tests d'épreuve utilisés pour provoquer des processus émotionnels spécifiques dans l'anxiété et la dépression. Cet article donne des exemples dans chacun de ces domaines. La caractérisation des patients et l'évolution des différents types de traitement deviendront encore plus importants dans le futur, avec l'espoir de développer des stratégies thérapeutiques plus personnalisées.

13. Kellner M, Knaudt K, Jahn H, Holsboer F, Wiedemann K. Atrial natriuretic hormone in lactate-induced panic attacks: mode of release and endocrine andpathophysiological consequences. *J Psychiatr Res*. 1998;32:37-48.

14. Kellner M, Muhtz C, Demiralay C, et al. The selective serotonin reuptake inhibitor excitalopram modulates the panic response tocholecystokinin tetrapeptide in healthy men depending on 5-HTTLPR genotype. *J Psychiatr Res*. 2009;43:642-648.

15. Harmer CJ, Cowen PJ, Goodwin GM. Efficacy markers in depression. *J Psychopharmacol*. In press.

16. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389.

17. Risch N, Herrel R, Lehner T, Liang KY, et al. Interaction between the serotonin transporter gene 5-HTTLPR), stressful life events, and riskof depression: a meta-analysis. *JAMA.* 2009;301:2462-2471.

18. Fergusson DM, Horwood LJ, Miller AL, Kennedy MA. Life stress, 5-HTTLPR and mental disorder: findings from a 30-year longitudinal study. *Br J Psychiatry*. 2011;198:129-135.
19. Ising M, Lucae S, Binder EB, Bettecken T, et al. A genomewide association study points to multiple loci that predict antidepressant drugtreatment outcome in depression. *Arch Gen Psychiatry*. 2009;66:966-975.
20. Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. *Psychiatr Serv*. 2009;60:1446-1457.
21. Horstmann S, Lucae S, Menke A, et al. Polymorphisms in GRIK4, HTR2A, and FKBP5 show interactive effects in predicting remission to antidepressant treatment. *Neuropsychopharmacology*. 2010;35:727-740.
22. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78:804-814.
23. Domschke K, Lawford B, Laje G, et al. Brain-derived neurotrophic factor (BDNF) gene: no major impact on antidepressant treatment response. *Int J Neuropsychopharmacol*. 2010;13:93-101.
24. Jacob C, Domschke K, Gajewska A, Warrings B, Deckert J. Genetics of panic disorder: focus on association studies and therapeutic perspectives. *Expert Rev Neurother*. 2010;10:1273-1284.
25. Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. *Am J Psychiatry*. 2008;165:6176-20.
26. Zoumakis E, Chrousos GP. Corticotropin-releasing hormone receptor antagonists: an update. *Endocr Dev*. 2010;17:36-43.
27. Allen NC, Bagade S, McQueen MB, Ioannidis JP, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet*. 2008;40:827-834.
28. Hennah W, Porteous D. The DISC1 pathway modulates expression of neurodevelopmental, synaptogenic and sensory perception genes. *PLoS One.* 2009;4:e4906.
29. Foster A, Miller del D, Buckley P. Pharmacogenetics and schizophrenia. *Clin Lab Med*. 2010;30:975-993.
30. McClay JL, Adkins DE, Aberg K, et al. Genome-wide pharmacogenomic analysis of response to treatment with antipsychotics. *Mol Psychiatry*. 2011;16:76-85.
31. Kirchheiner J, Seeringer A, Viviani R. Pharmacogenetics in psychiatry-a useful clinical tool or wishful thinking for the future? *Curr Pharm Des*. 2010;16:136-144.
32. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther*. 2007;116:496-526.
33. Kirchheiner J, Rodriguez-Antona C. Cytochrome P450 2D6 genotyping: potential role in improving treatment outcomes in psychiatric disorders. *CNS Dr*ugs. 2009;23:181-191.
34. Arranz MJ, Kapur S. Pharmacogenetics in psychiatry: are we ready for widespread clinical use? *Schizophr Bull*. 2008;34:1130-1144.
35. Hiemke C. Therapeutic drug monitoring in neuropsychopharmacology: does it hold its promises? *Eur Arch Psychiatry Clin Neurosci*. 2008;258(Suppl 1):21-27.
36. Fleeman N, Dundar Y, Dickson R, et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. *Pharmacogenomics J*. 2011;11:1-14.
37. Ozaki N. Pharmacogenetics of antipsychoatics. *Nagoya J Med Sci*. 2004;671-2:1-7.
38. Filiou MD, Turck CW, Martins-de-Souza D. Quantitative proteomics for investigating psychiatric disorders. *Proteomics Clin Appl*. 2011;5:38-49.
39. Martins-de-Souza D, Maccarrone G, Wobrock T, et al. Proteome analysis of the thalamus and cerebrospinal fluid reveals glycolysis dysfunction and potential biomarkers candidates for schizophrenia. *J Psychiatr Res*. 2010;44:1176-1189.
40. Raedler TJ, Wiedemann K. CSF-studies in neuropsychiatric disorders. *Neuro Endocrinol Lett*. 2006;27:297-305.
41. Mischak H, Schanstra JP. CE-MS in biomarker discovery, validation, and clinical application. *Proteomics Clin Appl*. 2011;5:9-23.
42. Refojo D, Holsboer F. CRH signaling. Molecular specificity for drug targeting in the CNS. *Ann N Y Acad Sci*. 2009;1179:106-119.
43. Locatelli V, Bresciani E, Tamiazzo L, Torsello A. Central nervous system-acting drugs influencing hypothalamic-pituitary-adrenal axis function. *Endocr Dev*. 2010;17:108-120.
44. Wiedemann K, Jahn H, Yassouridis A, Kellner M. Anxiolyticlike effects of atrial natriuretic peptide on cholecystokinin tetrapeptide-induced panic attacks: preliminary findings. *Arch Gen Psychiatry*. 2001;58:371-377.
45. Demiralay C, Jahn H, Kellner M, Yassouridis A, Wiedemann K. Influence of exogenous atrial natriuretic peptide on the nocturnal hypothalamic-pituitary-adrenal axis and sleep in healthy men. *Psychoneuroendocrinology*. 2010;35:1438-1445.
46. De Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaption to disease. *Nat Rev Neurosci*. 2005;6:463-475.
47. Marques AH, Silverman MN, Sternberg EM. Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. *Ann N Y Acad Sci*. 2009;1179:1-18.
48. Ising M, Horstmann S, Kloiber S, et al. Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression - a potential biomarker? *Biol Psychiatry*. 2007;62:47-54.
49. Schüle C, Baghai TC, Eser D, et al. The combined dexamethasone/CRH Test (DEX/CRH test) and prediction of acute treatment response in major depression. *PLoS One*. 2009;4:e4324.
50. Paslakis G, Heuser I, Schweiger U, Deuschle M. A single DEX/CRH test in male drug-free depressed patients is associated with the clinical response to treatment with fluoxetine. *J Psychiatr Res*. 2010;44:1154-1157.
51. Ising M, Künzel HE, Binder EB, Nickel T, Modell S, Holsboer F. The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:1085-1093.
52. Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF. Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology*. 2006;31:628-636.
53. Jahn H, Schick M, Kiefer F, Kellner M, Yassouridis A, Wiedemann K. Metyrapone as additive treatment in major depression: a double-blind and placebo-controlled trial. *Arch Gen Psychiatry*. 2004;61:1235-1244.
54. Friess E, Schmid D, Modell S, et al. Dex/CRH-test response and sleep in depressed patients and healthy controls with and without vulnerability for affective disorders. *J Psychiatr Res*. 2008;42:1154-1162.
55. Rao U, Hammen CL, Poland RE. Risk markers for depression in adolescents: sleep and HPA measures. *Neuropsychopharmacology*. 2009;34:1936-1945.
56. Murck H, Nickel T, Künzel H, et al. State markers of depression in sleep EEG: dependency on drug and gender in patients treated with tianeptine or paroxetine. *Neuropsychopharmacology*. 2003;28:348-358.
57. Nutt D, Lawson C. Panic attacks: a neurochemical overview of models and mechanisms. *Br J Psychiatry*. 1992;160:165-178.
58. Kellner M, Herzog L, Yassouridis A, Holsboer F, Wiedemann K. Possible role of atrial natriuretic hormone in pituitary-adrenocortical unresponsiveness in lactate-induced panic. *Am J Psychiatry*. 1995;152:1365-1367.
59. Gilles C, Luthringer R. Pharmacological models in healthy volunteers: their use in the clinical development of psychotropic drugs. *J Psychopharmacol*. 2007;21:272-282.
60. Shlik J, Aluoja A, Vasar V, Vasar E, Podar T, Bradwejn J. Effects of citalopram treatment on behavioural, cardiovascular and neuroendocrine response to cholecystokinin tetrapeptide challenge in patients with panic disorder. *J Psychiatry Neurosci*. 1997;22:332-340.
61. Zwanzger P, Eser D, Aicher S, et al. Effects of alprazolam on cholecystokinin-tetrapeptide-induced panic and hypothalamic-pituitary-adrenal-axis activity: a placebo-controlled study. *Neuropsychopharmacology*. 2003;28:979-984.
62. Zwanzger P, Rupprecht R. Selective GABAergic treatment for panic? Investigations in experimental panic induction and panic disorder. *J Psychiatry Neurosci*. 2005;30:167-175.
63. Kramer MS, Cutler NR, Ballenger JC, et al. A placebo-controlled trial of L-365,260, a CCKB antagonist, in panic disorder. *Biol Psychiatry*. 1995;37:462-466.
64. van Megen HJ, Westenberg HG, den Boer JA, Slaap B, van Es-Radhakishun F, Pande AC. The cholecystokinin-B receptor antagonist CI-988 failed to affect CCK-4 induced symptoms in panic disorder patients. *Psychopharmacology (Berl).* 1997;129:243-248.

65. Gong Q, Wu Q, Scarpazza C, Lui S, et al. Prognostic prediction of therapeutic response in depression using high-field MR imaging. *Neuroimage*. 2011;55:1497-1503.
66. Dager SR, Corrigan NM, Richards TL, Posse S. Research applications of magnetic resonance spectroscopy to investigate psychiatric disorders. *Top Magn Reson Imaging*. 2008;19:81-96.
67. Preter M, Klein DF. Panic, suffocation false alarms, separation anxiety and endogenous opioids. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:603-612.
68. Eser D, Leicht G, Lutz J, et al. Functional neuroanatomy of CCK-4-induced panic attacks in healthy volunteers. *Hum Brain Mapp*. 2009;30:511-522.
69. Nord M, Farde L. Antipsychotic occupancy of dopamine receptors in schizophrenia. *CNS Neurosci Ther*. In press.
70. Vyas NS, Patel NH, Nijran KS, Al-Nahhas A, Puri BK. The use of PET imaging in studying cognition, genetics and pharmacotherapeutic interventions in schizophrenia. *Expert Rev Neurother*. 2011;11:37-51.